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19 February 2009

(54) Title: METHODS AND COMPOSITIONS FOR MULTIPLE DISPLACEMENT AMPLIFICATION OF NUCLEIC ACIDS

(57) Abstract: Disclosed are methods for multiple displacement amplification of a nucleic acid sequence in a sample. The nucleic acid is contacted with a reaction mixture that includes a set of oligonucleotide primers and a plurality of polymerase enzymes. The reaction mixture is subjected to conditions under which the nucleic acid sequence is amplified to produce an amplification product in a multiple displacement amplification reaction. Also disclosed are kits containing a set of oligonucleotide primers with random sequences having lengths of 6 to 8 nucleobases. At least some of the individual members of the primers have one or more ribose modifications that stabilize or lock the ribose ring in a 3'-endo conformation. At least some of the primers have one or more universal nucleobases.



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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2008/065332**A. CLASSIFICATION OF SUBJECT MATTER***C12Q 1/68(2006.01)i, C12N 15/09(2006.01)i, C07H 21/00(2006.01)i*

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 8 C12Q 1/68

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

NCBI PubMed, eKIPASS, "multiple displacement amplificatio, polymerase, random primer, compatible solute, betaine, trehalose, etc."

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y A	US 6977148 B2 (Qiagen GmbH, DE) 20 December 2005 - see the whole document, especially Col. 2-3; Col. 9-11; Claims.	1-14, 16-19, 37 15, 20-30, 32 56, 58
X Y A	US 2003/0228613 A1 (Carole Bornarth, et al., US) 11 December 2003 - see the whole document, especially Claims.	1-14, 16-19, 37 15, 20-30, 32 56, 58
A	US 2005/0130216 A1 (Michael M. Becker, Gary P. Schroth, US) 16 June 2005 - see the whole document.	1-30, 32, 37, 56, 58
Y	Andrej-Nikolai Spiess, et al., 'Trehalose is a potent PCR enhancer: Lowering of DNA melting temperature and thermal stabilization of Taq polymerase by the disaccharide trehalose', In: Clinical Chemistry, 2004, Vol.50(7), 1256-1259 - see the whole document, especially Table 1.	15, 20-30, 32

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

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Name and mailing address of the ISA/KR

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2008/065332

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 31, 33-36, 38-55, 57, 59, 60
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Extra sheet

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

Box No.II. 2

Claims 31, 33–36, 38–55, 57, 59 and 60 are not clear and concise as required by PCT Article 6. The reason is as follows:

- 1) Claim 31 quotes claim 16, describing a reaction mixture for MDA. But claim 16 does not mention a reaction mixture for MDA.
- 2) Claims 33–36 quote claim 18, describing a reaction mixture for MDA. But claim 18 does not mention a reaction mixture for MDA.
- 3) Claims 38, 39, 44, 50, 54 and 55 quote claim 35, describing a kit for MDA. But claim 35 does not mention a kit for MDA.
- 4) Claims 47 quotes claim 33, describing a kit for MDA. But claim 33 does not mention a kit for MDA.
- 5) Claim 57 quotes claim 55, describing an oligonucleotide primer. But claim 55 does not mention an oligonucleotide primer.
- 6) Claims 38–55, 59 and 60 are also unclear because these claims quote indefinite claims.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2008/065332

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